

Correspondence

Reply

To the Editor:

In response to the comment by Kette and Smith,¹ this correspondence clarifies the methods used for efficacy assessment and provides additional evidence that a potential unblinding/placebo effect does not affect the conclusions from multiple trials showing that the grass allergy immunotherapy tablet (AIT) investigated is efficacious.

Kette and Smith¹ suggest that the clinical effect of the AIT treatment investigated in our trials²⁻⁵ is a placebo effect because of compromised blinding based on the local application-site reaction (ASR) experience. It is acknowledged that compromised blinding might be an issue with patient-reported outcome-based end points. Therefore, the symptom score has been compared for the entire placebo group and for the AIT subgroup that did not report any treatment-related adverse events. If the difference in symptom scores was due to subjects guessing their treatment allocation, these 2 groups would be expected to report a similar symptom score. Similarly, compromised blinding should be revealed when comparing symptom scores between subjects reporting local ASRs and subjects with no reported local ASRs. As seen in Fig 1, none of this is observed. Instead, the treatment effect is still clearly observed, even when comparing only groups with comparable local ASR patterns. The difference in symptom score area under the curve between the 2 groups during the grass pollen season was -8.58 (-23.1%). This difference corresponds to an average difference of -0.95 on the symptom score scale commensurate with the treatment effect relative to placebo in the entire treated group. Also, there is no difference in symptom scores between the groups with and without local ASRs.

Furthermore, compromised blinding might lead to differential dropout because of a lack of efficacy in the placebo group. This was not observed in any of trials,²⁻⁸ even in the recently completed 5-year trial⁹ for which the cited publication by Dahl et al⁵ presents the data from the first season.

As noted by Kette and Smith,¹ a score difference in the primary end points was observed between the placebo and AIT groups before the start of the season. The reason for preseasonal differences is the definition of the pollen season. The start of the season was defined as 3 consecutive days with a grass pollen count of 10 grains/m³.^{2-4,6-8} However, grass pollen is present in the air before the defined start of the season, as seen from the pollen curves.^{2,3,5} This leads to preseason separation of the symptom scores for the placebo and AIT groups, confirming an AIT treatment effect. The curves coincide at the extremes of the registration period (ie, at days -30 and 80 for the trial by Dahl et al⁵), which would not be observed without a true treatment effect. As noted in previous publications, the difference between the AIT and placebo groups is largest when the pollen count is highest (peak season), which is defined as the 15-day period with the highest cumulative pollen count.^{2,4,7,8}

In conclusion, a potential compromise of blinding because of local ASRs in the AIT trials does not change the overall treatment effect that has been observed to be dependent on the level of exposure and might hence be interpreted as an allergen-specific effect.

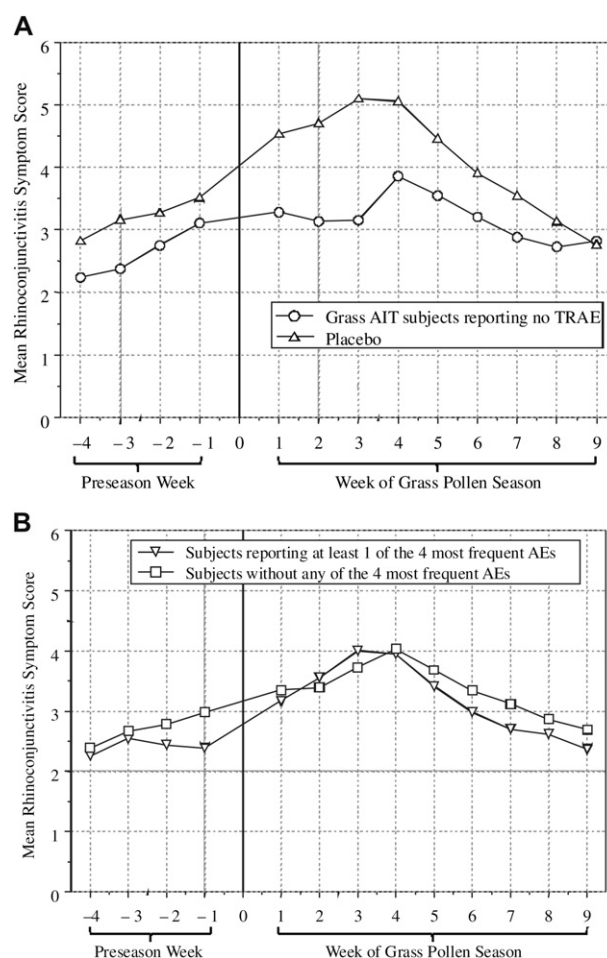


FIG 1. Pooled data from 4 trials²⁻⁵ assessed *post hoc* ($n = 1671$). **A**, Symptom scores for the entire placebo group ($n = 840$) and for the subgroup of subjects receiving active treatment who did not report any treatment-related adverse events (TRAE; $n = 139$). **B**, Symptom scores for subjects receiving active treatment who did not report any of the 4 most common adverse events (AEs; oral pruritus, throat irritation, mouth edema, and ear pruritus; $n = 387$) and for subjects with at least 1 of the 4 most common local reactions ($n = 444$).

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Disclosure of potential conflict of interest: M. Blaiss is a consultant for GlaxoSmithKline, Venture, and Sanofi-Aventis; is a speaker for Merck, AstraZeneca, ISTA, Sepracor, Proctor & Gamble, Alcon, Meda, and Nycomed; has served as an expert witness on the topics of patent antihistamine and wrongful death of a child; and is Treasurer of the Respiratory & Allergic Disease Foundation. H. S. Nelson is a consultant and/

or on advisory boards for Genentech, Novartis, Merck, Sepracor, Forest Labs, Pfizer, Planet BioPharma, AstraZeneca, Abbott Labs, DBV Technologies, and Ventura and has received research support from ALK-Abelló. S. R. Durham has provided lectures and consultancy for ALK-Abelló and GlaxoSmithKline; has provided consultancy for Circassia Ltd; and has received research support from ALK-Abelló and Novartis. R. Dahl has received remuneration, such as honoraria or consulting fees, from Boehringer Ingelheim, AstraZeneca, GlaxoSmithKline, ALK-Abelló, Airsonett, Pfizer, MSD, Novartis, and TEVA; has received research support from ALK-Abelló, Stallergenes, Pfizer, Boehringer Ingelheim, AstraZeneca, Novartis, Airsonett, and GlaxoSmithKline; is president of the Danish Respiratory Society; and is Vice Chair of the Global Alliance Against Chronic Respiratory Diseases. A. Bufe is a member of Protectimmun GmbH and has served as a consultant for ALK-Abelló, Denmark; Netstap Forschungs GmbH, Germany; and Bitop AG, Germany.

REFERENCES

1. Kette F, Smith W. Sublingual immunotherapy: allergen specific or placebo effect? *J Allergy Clin Immunol* 2011; ■■■:■■■.
2. Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R, Skoner DP. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. *J Allergy Clin Immunol* 2011;127:64-71, e4.
3. Nelson HS, Nolte H, Creticos P, Maloney J, Wu J, Bernstein DI. Efficacy and safety of timothy grass allergy immunotherapy tablet treatment in North American adults. *J Allergy Clin Immunol* 2011;127:72-80, e2.
4. Bufe A, Eberle P, Franke-Beckmann E, Funck J, Kimmig M, Klimek L, et al. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J Allergy Clin Immunol* 2009;123:167-73, e7.
5. Dahl R, Kapp A, Colombo G, de Monchy JG, Rak S, Emminger W, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;118:434-40.
6. Dahl R, Stender A, Rak S. Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. *Allergy* 2006;61:185-90.
7. Durham SR, Birk AO, Andersen JS. Days with severe symptoms: an additional efficacy endpoint in immunotherapy trials. *Allergy* 2011;66:120-3.
8. Durham SR, Yang WH, Pedersen MR, Johansen N, Rak S. Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;117:802-9.
9. Durham SR, Dahl R, Kapp A, Colombo G, DeMonchy JGR, Rak S, et al. Sustained, disease-modifying effect of grass allergen tablet immunotherapy 2 years after end of treatment. Paper presented at: European Academy of Allergology and Clinical Immunology; June 5-9, 2010; London, United Kingdom.

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